

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Legionnaires' Disease Treatment

Jorge F. Velazco

Abstract

Legionnaires' disease is an important cause of community-acquired pneumonia as well as hospital-acquired pneumonia. *Legionella pneumophila* is an important but uncommon respiratory pathogen with significant morbidity and mortality. Initially recognized as a fatal cause of pneumonia in the 1970s. Untreated Legionnaires' disease conveys high mortality, therefore a prompt treatment with appropriate antibiotics is of extreme importance. Currently, therapeutic options include macrolides and fluoroquinolones mainly, that have an effective therapeutic profile. Potential issues of bacterial resistance have risen, but overall, this is not a significant limitation of therapy. In addition, attempts to identify other cases related to the case will help find potential sources.

Keywords: *Legionella pneumonia*, *Legionella pneumophila*, Legionnaires' disease, Legionellosis, antimicrobial therapy

1. Introduction

Legionella pneumophila is responsible for 90% of Legionnaires' disease (LD) [1–3]. *Legionella pneumonia*, or LD has an increasing incidence, its mortality has progressively improved from 34% in 1980, to 12% in 1998, to 3.1% in 2010, however 20–25% of patients require mechanical ventilation with a mortality rate as high as 25% [4]. It is believed that the evolution of antibiotic therapy has improved outcomes [4]. *Legionella pneumonia* may have an atypical presentation that will contribute to its underdiagnosing and under-reporting [5], majority of reported cases are due to *Legionella pneumophila* serotype-1 (80%), that may reflect the relatively wide availability of commercial kits to test for this specific serotype [5]. *Legionella* is an ubiquitous environmental intracellular Gram-negative bacteria, therefore antibiotics capable of penetrating phagocytic cells should be selected, then macrolides and quinolones have become the recommended therapies [6–8]. Risk factors associated with higher mortality rates are older age, smoking, chronic cardiopulmonary disease, diabetes, alcohol abuse, cancer and immunosuppression [9]. Appropriate antibiotic selection will drop mortality significantly, from 60–70% to 10–20% [2, 7, 10, 11].

2. Treatment

For years, macrolides, specifically erythromycin, has been the mainstay of therapy until the 1990s [4, 12], however with the emergence of newer macrolides and quinolones, the therapeutic selection has shifted, and now Azithromycin or Levofloxacin are considered the mainstay of LD treatment [12]. Beta-lactam and

aminoglycoside antibiotics are ineffective in the treatment of LD, then empiric therapy based on either macrolides or quinolones for initial moderate to severe pneumonia will be a reasonable approach [12–14].

Effective antibiotic therapy depends on the ability to concentrate in alveolar macrophages, and for these concentrations to be effective, it will need to range from 10 to 30 times greater than serum concentrations [15] Fluoroquinolones are antimicrobials with concentration-dependent bactericidal activity [16].

In cases of severe LD, combination therapy has been advocated without evidence of superiority [12]. The incidence of LD as cause of severe pneumonia requiring ICU admission has been reported as high as second most common behind *Streptococcus pneumonia* (17.8 versus 21.6%, respectively) [2, 13].

In a retrospective review of 3157 adult cases, from more than 400 U.S. hospitals between 2008 and 2013, it was noted that quinolones alone were used in 28.8%, whereas azithromycin alone was used in 34% of patients, only 1.8% of patients received combination therapy (see **Figure 1**). Hence, the majority of patients with LD in the US are treated with azithromycin and/or quinolone [4]. No prospective randomized trial has compared outcomes of levofloxacin versus azithromycin [14].

2.1 Empiric therapy

The choice of empiric antibiotic therapy is based on the premise of providing optimal therapy, the epidemiological features of the probable agents, and an inference of the most likely pathogen [17].

The empirical coverage for Legionnaires’ disease is still a matter of debate, in view of low testing frequency that underscores poor emphasis on *Legionella* role in pneumonia [18]. The incidence of LD is higher in cases of severe pneumonia, hence patients admitted to an ICU setting should be tested and treated as potential *Legionella pneumonia* [17]. Historically empirical optimal monotherapy treatment has been based on doxycycline, a quinolone or azithromycin [19].

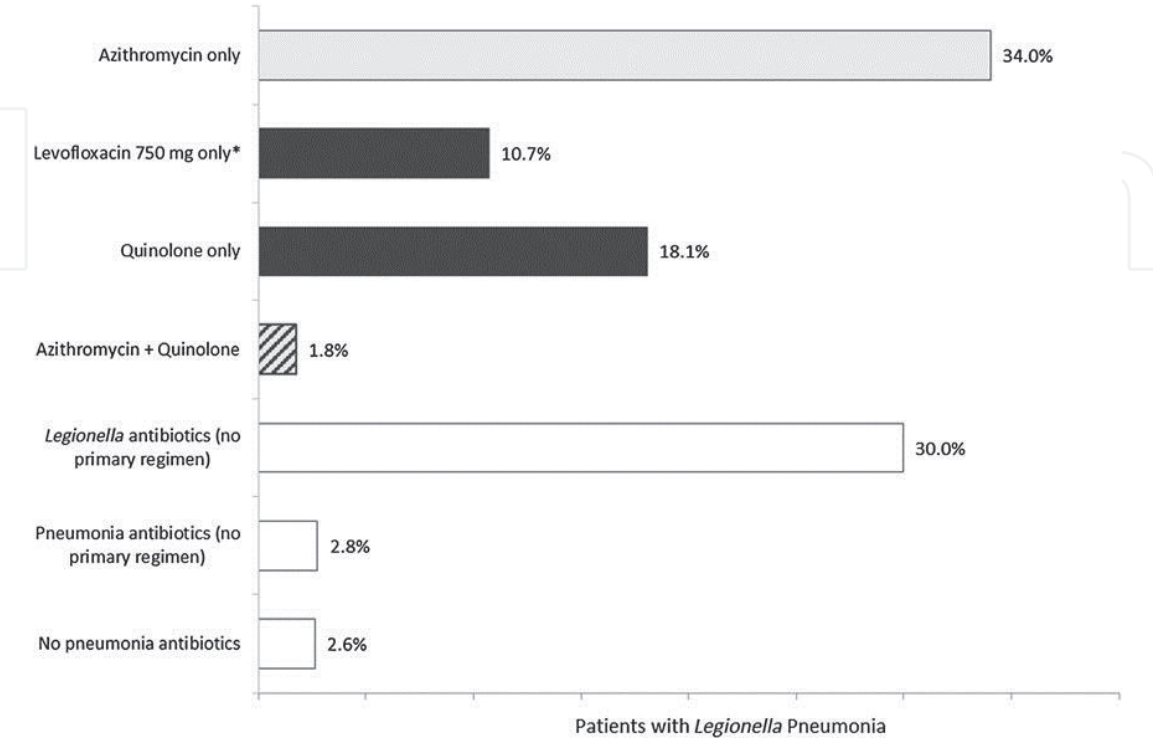


Figure 1.
In-hospital treatment strategies for patients with Legionnaires’ disease. Adapted from Ref. [4].

Respiratory fluoroquinolones are an effective empiric treatment for bacterial community-acquired pneumonia, used as monotherapy in the outpatient setting, and hospitalized patients, as a first-line or alternative agents; in addition to be used as combination therapy in the ICU setting [20]. Azithromycin has a comparable antibiotic profile to fluoroquinolones, in addition has a favorable safety profile, higher intracellular concentrations and longer post antibiotic effect [21].

In a prospective observational study of 3934 hospitalized patients by Viasus et al., performed in Spain at a tertiary teaching hospital between 1995 and 2010, 214 (5.4%) patients were diagnosed with LD, and 24 patients (11.2% of the LD patients) received inappropriate empirical antibiotic therapy; among the other 190 patients, 111 received levofloxacin, 74 patients received macrolides, and three combination of quinolones and macrolides, 1 doxycycline and 1 clindamycin [22] (Table 1).

2.2 Targeted therapy

Early, targeted therapy that covers LD has shown to improve overall outcomes [19]. The most frequently identified of LD is *Legionella pneumophila* serogroup 1 in 80% of cases [23]. New diagnostic test had been added to the testing armamentarium (urinary antigen and polymerase chain reaction). Empirical therapy should be replaced by targeted therapy as soon as *Legionella* has been identified [17].

Garcia-Vidal et al. reported an observational cohort in Spain of all patients admitted with community acquired pneumonia from 2000 to 2014, 446 patients were diagnosed with LD; 335 patients (75.1%) received appropriate initial therapy with either quinolones, macrolides, combination with rifampin, or combination macrolide and quinolones. Primary outcome was overall 30-day in-hospital mortality. Thirty-six patients were excluded, 175 patients received levofloxacin, 177 patients received azithromycin and 58 patients received clarithromycin, without statistical significant difference for in-hospital 30-day mortality between the cohorts [24].

Once LD has been diagnosed, some experts suggest combined therapy instead of monotherapy for severe pneumonia, although there is no solid evidence support it [13]. In a retrospective observational multicenter Spanish series of 779 ICU patients admitted to the ICU with severe pneumonia, 25 patients (3.2%) were found to have LD, and prescription of monotherapy versus combination therapy was not

Mild disease ambulatory setting	Moderately severe disease	Severe disease intensive care unit setting
Doxycycline 100 mg orally q12h x 14d	Doxycycline 200 mg IV q12h x 72h, then 100 mg IV q12h x 11d	Doxycycline 200 mg IV q12h x 14d
Levofloxacin 500 mg orally q24h x 14d	Moxifloxacin 400 mg IV q24h x 14d	Levofloxacin 500 mg IV q24h x 14d
Moxifloxacin 400 mg orally q24h x 14d	Tigecycline 200 mg IV x 1dose, then 100 mg IV q24h x 14d	Moxifloxacin 400 mg IV q24h x 14d
Azithromycin 500 mg orally x 1dose, then 250 mg orally q24h x 10d		TMP-SMX 5 mg/kg IV q6h x 14d or Rifampin 300 mg orally q12h x 14d, maybe used as a second drug

Adapted from Ref. [15].

Table 1.
Empiric therapy for Legionnaires' disease.

protocolized, with ICU mortality as primary endpoint; it was found that there was no statistical significant difference of overall ICU mortality among both treatment groups; however if the severe pneumonia was associated to shock the difference became statistically significant [13].

2.3 Antibiotic selection and duration

There may be a role for a specific antibiotic choice based on severity of illness: need for intensive care unit (ICU) admission, need for invasive mechanical ventilation [4]. Dose and route of antibiotic delivery will be dictated by the severity, level of consciousness, and gastrointestinal function integrity [12]. Most of the antibiotics are available in oral presentations with excellent bioavailability (>90%), therefore transition among IV to oral regimens is seamless [19].

Despite absence of evidence, initial levofloxacin dose is recommended at 750 mg daily, and azithromycin 500 mg daily [14].

Levofloxacin use was associated with a shorter length of stay in the hospital, and shorter time to reach clinical stability [22]; moreover a small retrospective series showed no inferiority of ciprofloxacin to erythromycin in Japan [25]. In a retrospective single-center study at University of Michigan from 1999 to 2011, 41 patients with LD were analyzed after been treated with azithromycin versus fluoroquinolones, comparing clinical outcomes: all-cause mortality, length of stay in the hospital, time to clinical stability and development of complications, showing no significant differences among the two therapies [19, 21] (Table 2).

Duration of therapy is important to provide cure and prevent relapse [19]. The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) recommend that patients with LD to be treated for 5–14 days, shorter courses maybe appropriate if Azithromycin is the antibiotic of choice. Treatment should not be stopped until patients are afebrile for 48–72 hours [22].

Therapy	Normal adult dose	Comments
Macrolides	Azithromycin 500 mg IV q24h or clarithromycin 500 mg IV q12h	Preferred regimen in most settings, or a fluoroquinolone
Fluoroquinolones	Levofloxacin 500 mg IV q24h or moxifloxacin 400 mg IV q24h	Generally well tolerated and effective
Rifampin	300–600 mg IV q12h	Multiple drug interactions, including warfarin, opiates, cyclosporine, antiretroviral protease inhibitors; used with a macrolide or quinolone
Doxycycline	200 mg IV × 1dose, then 100 mg IV q12h	Limited clinical experience shows activity
Combinations	Levofloxacin 500 mg IV q24h or another fluoroquinolone + azithromycin 500 mg IV q24h; consider adding rifampin to monotherapy	No clear evidence of efficacy of combination therapy compared with monotherapy; often used in severe extensive disease in high-risk patients falling monotherapy

Adapted from Ref. [19].

Table 2.
Therapeutic options for severe Legionnaires’ disease.

Immunocompromised patients have a higher incidence of LD; cavitation, empyema, extrapulmonary disease may occur; and urinary antigen is less sensitive. In this population an antibiotic combination, and longer course maybe indicated (21 days) [3], and despite this this population has a higher mortality rate than matched groups [26]. An extended course up to 21 days is recommended for immunocompromised patients, severe disease, extrapulmonary manifestations, and inappropriate initial therapy [14].

Combination therapy has included different regimens: rifampin-clarithromycin; clarithromycin-ciprofloxacin-rifampin, and clarithromycin-levofloxacin-rifampin [13].

Older macrolides will interact with drugs like tacrolimus and ciclosporin through the cytochrome P-450 enzyme system, then quinolones, doxycycline or azithromycin maybe used in transplanted hosts [14].

2.4 Therapy outcome

Early initiation of appropriate antibiotics, improves outcomes, therapy with quinolones within 8 hours of ICU admission reduces mortality [5, 19].

In the Viasus' Spanish series, 41 (19.1%) patients with LD developed severe disease (ICU admission or death), independent factors were identified in this group: current/former smoker, macrolide use, initial inappropriate antibiotic therapy and high risk pneumonia severity index (PSI) class. The overall cure rate is 95% at 10–14 days after therapy [22] (Table 3).

In a Portuguese observational series, it was noted that patient with severe LD complicated by refractory respiratory failure were able to be supported by extra corporeal membrane oxygenation (ECMO) with high survival rates (86%); those patients had a faster clinical deterioration with very early ECMO initiation [27]. In a retrospective case review from University of Michigan between 1994 and 2006, survival rates were also noted to be high (67%) [28].

Antibiotic resistance is always a concern, it was noted that acquired resistance to macrolides, fluoroquinolones or rifampin could be easily selected in vitro; however in clinical practice, antibiotic susceptibility testing is not commonly performed [29], due to the fact that *Legionella pneumophila* serogroup 1 strains did not show any in vitro resistance towards eight antibiotics tested by Vandewalle-Capo et al.

Therapy and outcome	<i>L. pneumophila</i> pneumonia (n = 214)	<i>S. pneumonia</i> pneumonia (n = 1346)	P
Inappropriate antibiotic therapy	24 (11.2)	8 (0.6)	<0.001
In-hospital complications	74 (34.6)	460 (34.3)	0.92
ICU admission	38 (17.8)	151 (11.2)	0.007
Need for mechanical ventilation	26 (12.4)	122 (9.2)	0.14
Time to clinical stability, median (IQR), d	3.5 (2–5)	4 (2–6)	0.85
Length of hospital stay, median (IQR), d	9 (6–13)	8 (6–12)	0.14
Length of intravenous therapy, median (IQR), d	4 (2–6)	5 (3–7)	<0.001
In-hospital case-fatality rate	13 (6.1)	103 (7.8)	0.38

Adapted from Ref. [22].

Table 3.
Therapy and outcomes of patients with *L. pneumophila* and *S. pneumoniae* pneumonia.

(ciprofloxacin, moxifloxacin, levofloxacin, azithromycin, erythromycin, clarithromycin, rifampin and doxycycline) [1].

In a systematic review and meta-analysis comparing quinolones versus macrolides effectiveness against LD, non-significant difference was found, however all studied outcomes favored quinolones, like mortality, clinical cure, time to fever resolution, length of stay in the hospital. Twelve studies were included in the analysis, and the absence of significance maybe related to lack of statistical power [30].

3. Conclusion

Legionnaires' disease is a relative frequent cause of pneumonia syndromes, and it is associated to high morbidity and mortality [22], therefore a delay in starting appropriate therapy has been associated with increased mortality [17]. Consistent with current guidelines, antibiotic therapy should be based on either azithromycin or a quinolone to treat for *Legionella* pneumonia. Optimum therapy is not properly supported by clinical evidence, however in view of rare potential bacterial resistance to macrolides and quinolones, these antibiotic groups remain as mainstay of LD therapy.

Conflict of interest

The author declares no conflict of interest related to this topic.

Author details

Jorge F. Velazco

Department of Medicine, Texas A&M Health Science Center—College of Medicine, Baylor Scott and White Health-Memorial Hospital, Temple, Texas, USA

*Address all correspondence to: jorge.velazco@bswhealth.org

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Vandewalle-Capo M, Massip C, Descours G, et al. Minimum inhibitory concentration (MIC) distribution among wild-type strains of *Legionella pneumophila* identifies a subpopulation with reduced susceptibility to macrolides owing to efflux pump genes. *International Journal of Antimicrobial Agents*. 2017;**50**:684-689. DOI: 10.1016/j.ijantimicag.2017.08.001
- [2] Harris NJ, Harris AC, Spiro M. Management of *Legionella* in the intensive care setting. *BMJ Case Reports*. 2011;**2011**:1-7. DOI: 10.1136/bcr.2010.3587
- [3] Lanternier F, Ader F, Pilmis B, et al. Legionnaire's disease in compromised hosts. *Infectious Disease Clinics of North America*. 2017;**31**:123-135. DOI: 10.1016/j.idc.2016.10.014
- [4] Gershengorn HB, Keene A, Dzierba AL, et al. The association of antibiotic treatment regimen and hospital mortality in patients hospitalized with *Legionella pneumonia*. *Clinical Infectious Diseases*. 2015;**60**:e66-e79. DOI: 10.1093/cid/civ157
- [5] Sharma L, Losier A, Tolbert T, et al. Pneumonia updates on *Legionella*, *Chlamydia*, and *Mycoplasma pneumonia*. *Clinics in Chest Medicine*. 2017;**38**(1):45-58. DOI: 10.1016/j.ccm.2016.11.011
- [6] Miyashita N, Higa F, Aoki Y, et al. Clinical presentation of *Legionella pneumonia*: Evaluation of clinical scoring systems and therapeutic efficacy. *Journal of Infection and Chemotherapy*. 2017;**23**:727-732. DOI: 10.1016/j.jiac.2017.09.001
- [7] Beaute J. Legionnaires' disease in Europe, 2011 to 2015. *Euro Surveillance*. 2017;**22**(27):1-8. DOI: 10.2807/1560-7917.ES.2017.22.27.30566
- [8] Harrison CF, Kicka S, Trofimov V, et al. Exploring anti-bacterial compounds against intracellular *Legionella*. *PLoS ONE*. 2013;**8**(9):1-13. DOI: 10.1371/journal.pone.0074813
- [9] Cecchini J, Tuffet S, Sonnevile R, et al. Antimicrobial strategy for severe community-acquired legionnaires' disease: A multicenter retrospective observational study. *The Journal of Antimicrobial Chemotherapy*. 2017;**72**:1502-1509. DOI: 10.1093/jac/dkx007
- [10] Kakeya H, Ehara N, Fukushima K, et al. Severe Legionnaires's disease successfully treated using a combination of fluoroquinolone, erythromycin, corticosteroid, and sivelestat. *Internal Medicine*. 2008;**47**:773-777. DOI: 10.2169/internalmedicine.47.0677
- [11] Garcia-Vidal C, Carratala J. Current clinical management of Legionnaires' disease. *Expert Review of Anti-Infective Therapy*. 2006;**4**(6):995. DOI: 10.1586/14787210.4.6.995
- [12] Phin N, Parry-Ford F, Harrison T, et al. Epidemiology and clinical management of Legionnaires' disease. *The Lancet Infectious Diseases*. 2014;**14**:1011-1021. DOI: 10.1016/S1473-3099(14)70713-3
- [13] Rello J, Gattarello S, Souto J, et al. Community-acquired *Legionella pneumonia* in the intensive care unit: Impact on survival of combined antibiotic therapy. *Medicina Intensiva*. 2012;**37**(5):320-326. DOI: 10.1016/j.medint.2012.05.010
- [14] Cunha B, Burillo A, Bouza E. Legionnaires' disease. *Lancet*. 2016;**387**:376-385. DOI: 10.1016/S0140-6736(15)60078-2
- [15] Cunha CB, Cunha BA. Antimicrobial therapy for Legionnaires'

disease: Antibiotic stewardship implications. Infectious Disease Clinics of North America. 2017;**31**:179-191. DOI: 10.1016/j.idc.2016.10.013

[16] Obrink-Hansen K, Hardlei TF, Brock B, et al. Moxifloxacin pharmacokinetic profile and efficacy evaluation in empiric treatment of community-acquired pneumonia. Antimicrobial Agents and Chemotherapy. 2015;**59**:2398-2404. DOI: 10.1128/AAC.04659-14

[17] Diederer BM. *Legionella* spp. and Legionnaires' disease. The Journal of Infection. 2008;**56**:1-12. DOI: 10.1016/j.jinf.2007.09.010

[18] Gramegna A, Sotgiu G, Di Pasquale M, et al. Atypical pathogens in hospitalized patients with community-acquired pneumonia: A worldwide perspective. BMC Infectious Diseases. 2018;**18**:677. DOI: 10.1186/s12879-018-3565-z

[19] Chahin A, Opal SM. Severe pneumonia caused by *Legionella pneumophila*. Differential diagnosis and therapeutic considerations. Infectious Disease Clinics of North America. 2017;**31**:111-121. DOI: 10.1016/j.idc.2016.10.009

[20] Garau J, Fritsch A, Arvis P, et al. Clinical efficacy of moxifloxacin versus comparator therapies for community-acquired pneumonia caused by *Legionella* spp. Journal of Chemotherapy. 2010;**22**(4):264-266. DOI: 10.1179/joc.2010.22.4.264

[21] Nagel JL, Rarus RE, Crowley AW, et al. Retrospective analysis of azithromycin versus fluoroquinolones for the treatment of *Legionella pneumonia*. P&T: A Peer-reviewed Journal for Formulary Management. 2014;**39**(3):203-205

[22] Viasus D, Di Yacovo S, Garcia-Vidal C, et al.

Community-acquired *Legionella pneumophila* pneumonia. A single-center experience with 214 hospitalized sporadic cases over 15 years. Medicine. 2013;**92**:51-60. DOI: 10.1097/MD.0b013e31827f6104

[23] Ito A, Ishida T, Tachibana H, et al. A case of community-acquired pneumonia due to *Legionella pneumophila* serogroup 9 wherein initial treatment with single-dose oral azithromycin appeared useful. Japanese Journal of Infectious Diseases. 2017;**70**:660-662. DOI: 10.7883/yoken.JJID.20176.548

[24] Garcia-Vidal C, Sanchez-Rodriguez I, Simonetti AF, et al. Clinical Microbiology and Infection. 2017;**23**:653-658. DOI: 10.1016/j.cmi.2017.02.030

[25] Haranga S, Tateyama M, Higa F, et al. Intravenous ciprofloxacin versus erythromycin in the treatment of *Legionella pneumonia*. Internal Medicine. 2006;**46**:353-357. DOI: 10.2169/internalmedicine.46.6006

[26] Pedro-Botet ML, Garci-Cruz A, Tural C, et al. Severe Legionnaires' disease successfully treated with levofloxacin and azithromycin. Journal of Chemotherapy. 2006;**18**(5):559-561. DOI: 10.1179/joc.2006.18.5.559

[27] Roncon-Albuquerque R Jr, Vilares-Morgado R, van der Heijden GT, et al. Outcome and management of refractory respiratory failure with timely extracorporeal membrane oxygenation: Single-center experience with *Legionella pneumonia*. Journal of Intensive Care Medicine. 2019;**34**(4):344-350. DOI: 10.1177/0885066617700121

[28] Bryner B, Miskulin J, Smith C, et al. Extracorporeal life support for the adult respiratory distress syndrome due to severe *Legionella pneumonia*. Perfusion. 2014;**29**(1):39-43. DOI: 10.1177/0267659113497229

[29] Wilson RE, Hill RL, Chalker VJ, et al. Antibiotic susceptibility of *Legionella pneumophila* strains isolated in England and Wales 2007-12. The Journal of Antimicrobial Chemotherapy. 2018;73:2757-2761. DOI: 10.1093/jac/dky253

[30] Burdet C, Lepeule R, Duval X, et al. Quinolones versus macrolides in the treatment of legionellosis: A systematic review and meta-analysis. The Journal of Antimicrobial Chemotherapy. 2014;69:2354-2360. DOI: 10.1093/jac/dku159